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Running title: Aβ load and shapes of brain structures

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Abstract

Aβ deposition is a driving force of Alzheimer's disease pathology and can be detected early by amyloid positron emission tomography. Identifying presymptomatic structural brain changes associated with Aβ deposition might lead to a better understanding of its consequences and provide early diagnostic information. In this respect we analyzed measures of cortical thickness and subcortical volumes along with hippocampal, thalamic and striatal shape and surface area by applying novel analysis strategies for structural magnetic resonance imaging. We included 69 cognitively normal elderly subjects after careful clinical and neuropsychological workup. Standardized uptake value ratios (cerebellar reference) for uptake of 11-C-Pittsburgh Compound B (PiB) were calculated from positron emission tomographic data for a cortical measurement and for bilateral hippocampus, thalamus and striatum. Associations to shape, surface area, volume and cortical thickness were tested using

regression models that included significant predictors as covariates. Left anterior hippocampal shape was associated with regional PiB uptake ($p < 0.05$, FDR-corrected), whereas volumes of the hippocampi and their subregions were not associated with the cortical measurement or uptake in the other regions (all $p > 0.05$, FDR-corrected). Within the entorhinal cortical region of both hemispheres, thickness was negatively associated with cortical uptake ($p < 0.05$, FDR-corrected). Hence, localized shape measures and cortical thickness may be potential biomarkers of presymptomatic Alzheimer's disease.

Keywords: beta-amyloid; hippocampal shape; Alzheimer's disease; Magnetic resonance imaging; positron emission tomography

Introduction

Sporadic Alzheimer's disease (AD) is a major global health burden with no cure available at the moment. It has become evident that the pathological process may start decades before the onset of clinical symptoms (Villemagne *et al.*, 2013). Therefore diagnostic criteria have been developed to identify the preclinical stages of Alzheimer's disease (Sperling *et al.*, 2011) with the ultimate goal of facilitating studies on early intervention. Currently the A 4 trial examines if the antibody solanezumab may be beneficial in cognitively asymptomatic subjects selected on the basis of a positive amyloid-pet (Laske, 2014). It is hypothesized that intervention at presymptomatic stages is most effective treatment when cognitive functioning can be stabilized at the highest possible level (Masdeu *et al.*, 2012). Furthermore substances directed at Abeta-reduction are believed to be more effective if given early in the disease process. A scenario of early detection would require a high number of cognitively normal elderly individuals to undergo preventive screening. Hence, it is desirable to obtain diagnostic

measures non-invasively and at comparatively low cost. In this respect, magnetic resonance imaging (MRI) measurements capable of identifying early brain changes associated with amyloid deposition would pose an attractive option.

Highly localized structural MRI measures such as cortical thickness (CT) and subcortical shape and surface area (SA) of brain structures are necessary to detect highly spatially confined presymptomatic changes. Using CT analysis, a recent study presented results that are consistent with cortical thinning during progression from preclinical AD to dementia due to AD (Dickerson *et al.*, 2011). **Additionally, evidence for early thalamic abnormalities in Alzheimer's disease is growing (Aggleton et al., 2016). Previous studies have reported thalamic differences between normal-aging subjects and individuals with amnestic MCI using texture analysis (de Oliveira *et al.*, 2011) and smaller thalamic volume in MCI compared to controls with normal cognition (Yi *et al.*, 2016).** In a recent study from our group, we found thalamic and striatal shape differences between individuals with MCI and individuals with normal cognition in the absence of volumetric differences (Leh *et al.*, 2015). These findings suggest that thalamic shape changes occur early in AD and underline the importance of thalamic shape information in the search for presymptomatic AD biomarkers and point to an important role of **the anterior thalamic nuclei in AD research which play an important role in episodic memory. In contrast to thalamic shape, hippocampal morphology has already been studied repeatedly in AD (de Flores *et al.*, 2015) and studies comparing patients with AD to healthy control subjects have shown inward deformation of cornu ammonis (CA) 1 (Frisoni *et al.*, 2008; Wang *et al.*, 2003).** In one previous study, localized inward changes of left hippocampal surface significantly predicted progression of nondemented elderly individuals to dementia due to AD (Csernansky *et al.*, 2005).

In the current study, we therefore used structural MRI measures of CT and hippocampal, thalamic and striatal volume, shape and SA to identify brain changes associated with amyloid-deposition measured by Pittsburgh compound B (PiB) positron emission tomography (PET) in cognitively normal elderly individuals.

Materials and methods

Participants

A total of 69 cognitively healthy elderly participants (32 female, age 55-80 years) from a longitudinal cohort study were included. **17 of these participants have already been included in a previous publication from our group focusing on structural differences between individuals with amnestic MCI and cognitively normal subjects (Leh *et al.*, 2015).** Inclusion and exclusion criteria have been published previously (Steininger *et al.*, 2014; Schreiner *et al.*, 2014; Gietl *et al.*, 2015). Cognitive health was confirmed by clinical examination consisting of clinical workup and neuropsychological assessment and a Mini-Mental State Examination (MMSE) score of ≥27. Participants were excluded if one or more of the following conditions were met: contraindication against MRI or venipuncture, substance abuse with a possible effect on cognition, change in red blood cell count of clinical significance, allergy to PiB or one of its constituents, history of severe allergic reactions to drugs or allergens, critical or medically unstable illness, pregnancy or lactation, significant exposure to radiation.

Descriptive data for all metric control, volume and standardized uptake value ratio (SUVR) variables can be found in Table 1.

The study was conducted in compliance with the Helsinki Declaration and approved by the cantonal ethics committee of Zurich, Switzerland (E_64_2009). Written informed consent was obtained from each participant prior to study enrolment.

PET acquisition

The PET acquisition procedure has been previously published (Gietl *et al.*, 2015; Riese *et al.*, 2015; Steininger *et al.*, 2014). Each participant received an antecubital venous injection of approximately 350 MBq of PiB (PiB synthesis has been described before in Gietl *et al.*, 2015). A 70-minute dynamic PET scan (4x15, 8x30, 9x60, 2x180 and 10x300 seconds) was performed. Voxel spacing was 2.34 x 2.34 x 3.27 mm.

MR acquisition

MR acquisition has been published previously (Gietl *et al.*, 2015). T1-weighted data were acquired on a 3-T Phillips Achieva with the following parameters: repetition time 8.2 ms, echo time 3.7 ms, and 8° flip angle, field of view 240 mm (AP) x 220 mm (FH) x 188 mm (RL), 220 axial slices with 1-mm single-slice thickness (voxel dimensions: 0.94 x 0.94 x 1 mm).

Subcortical segmentation and volume calculation

Segmentation of bilateral hippocampus, thalamus and striatum as well as hippocampal subfields was performed by using the Multiple Automatically Generated Templates (MAGeT Brain) algorithm (Chakravarty *et al.*, 2013) using a voxel-wise majority vote (Collins *et al.*, 2010). The input atlases used for hippocampal subfield segmentation were produced by

Winterburn *et al.* (2013) and have been validated for use with MAGeT brain (Pipitone *et al.*, 2014). The five subfields delineated in these atlases are cornu ammonis (CA) 1, subiculum, CA 4 and dentate gyrus, CA 2 and 3, and stratum radiatum/lacunosum/moleculare (SRLM). We used five input atlases that were registered to a subset of 21 subjects, a number that had been shown to be optimal in previous research (Pipitone *et al.*, 2014), to generate a template library. The input atlas used for thalamus and striatum segmentation was produced by (Chakravarty *et al.*, 2006). **A visualization of the left-hemispheric part of these volumes of interest is displayed in Figure 1.**

For each subject, volumes of total hippocampi and their subfields were derived from the number of voxels resulting from segmentation. These volumes were then divided by the total intracranial volume of the subject and the resulting value was used for analysis. Calculation of total intracranial volume has been described previously (Buckner *et al.*, 2004).

Determination of cortical 11-C-PiB-SUVR (cortical SUVR from now on) as a measure of cortical plaque burden

Image processing was done automatically under visual control with PMOD PNEURO tool Version 3.4 (PMOD LTD, Zurich, Switzerland) and described in detail before (Gietl *et al.*, 2015). The average of the first 13 frames of the dynamic scans was co-registered with the structural MR image using a normalized mutual-information–based registration. After normalization, a maximum probability atlas (Hammers N30R83) (Gousias *et al.*, 2008; Hammers *et al.*, 2003) was used to define 48 VOIs based on the segmentation of GM and white matter. Segmentation was performed on the individual MRI (at least 50% GM probability). The combined transformation matrices (PET to MR and MR to Montreal Neurologic Institute [MNI] space) were applied to the dynamic

PET images to perform all further analyses in MNI space. The average tracer uptake 50-70 minutes was then calculated for the segmented grey matter VOIs. For derivation of cortical SUVR, 24 bilateral cortical brain structures of the Hammers N30R83 atlas (http://doc.pmod.com/pneuro/7674.htm) - excluding occipital lobe, insula, primary motor and sensorimotor cortices - were merged using a volume-weighted averaging procedure, ascertaining, that the uptake in larger regions contributes more to this average than the uptake in smaller regions. Bilateral cerebellar grey matter uptake, which was also derived from the Hammers N30R83 atlas, served as a reference for standardization between subjects because of the relatively late involvement of the cerebellar grey matter in plaque pathology, as done before (Johnson *et al.*, 2016; Liu *et al.*, 2015). The ratio of the cortical VOI's average uptake and the average cerebellar grey matter uptake is termed "cortical SUVR" and serves as a measure of cortical plaque burden.

Regional 11-C-PIB-SUVR (regional SUVR from now on) calculation

Image processing for regional SUVR calculation was done with PMOD FUSION tool Version 3.5 (PMOD LTD, Zurich, Switzerland). Also in this analysis the average of the first 13 frames was co-registered with the structural MR image using a normalized mutual-information–based registration.. Registration success was determined by visual inspection performed by our group. The regions specifically studied for shape changes within this project for hippocampal, thalamic and striatal SUVR calculation were derived from automatic subcortical segmentation with the MAGeT Brain algorithm as described above. This algorithm has been demonstrated to outperform FreeSurfer and FSL FIRST (Pipitone *et al.*, 2014). Segmentation was performed in subject space of the individual MR. The PET to MR transformation matrices from the registration process

were applied to the dynamic PET images to be able to place the MR derived regions on the PET image. Subsequent analyses were performed in subjects' MR space. Again, the average tracer uptake 50-70 minutes was then calculated for the segmented VOIs. The cerebellar reference region used for calculation of regional SUVR was segmented using the LONI probabilistic brain atlas (LPBA40) (Shattuck *et al.*, 2008). The ratio of the specific uptake of a particular VOI and the cerebellar grey matter uptake is termed "regional SUVR".

Shape and SA calculation

Delineation of bilateral hippocampus, thalamus and striatum and was carried out using a method adapted from Lerch *et al.* (2008) in order to measure local inward and outward displacements. For a detailed description, see Lerch *et al.* (2008) and Raznahan *et al.* (2014). SA calculation was performed as described previously (Raznahan *et al.*, 2014).

Cortical thickness calculation

CT was calculated with the CIVET pipeline (version 1.1.10, Montreal Neurological Institute at McGill University, Montreal, Quebec, Canada) (Ad-Dab'bagh *et al.*, 2006). First, the T1 image of each subject was linearly registered to the symmetric ICBM 152 template (Collins *et al.*, 1994; Mazziotta *et al.*, 1995). Then, skull stripping (Smith, 2002) and tissue segmentation into gray and white matter and cerebrospinal fluid (CSF) (Tohka *et al.*, 2004; Zijdenbos *et al.*, 1998) was carried out. Next, the interface between gray matter and CSF and the inner white matter surface were constructed for each hemisphere using deformable models (Kim *et al.*, 2005). For each of the resulting 40,962 vertices per hemisphere, the distance in millimeters between the inner and the outer surface was measured using a previously described method

(Lerch & Evans, 2005). In order to increase statistical power and signal-to-noise ratio, blurring was performed on the cortical thickness maps with a 20mm diffusion smoothing kernel (Chung & Taylor, 2004).

Data analysis

For statistical analysis, the R software package (https://www.r-project.org/) (R Core Team, 2015) was used. In addition, the RMINC (R for Medical Imaging NetCDF) library (https://wiki.mouseimaging.ca/display/MICePub/RMINC/) (Lerch & Nikelski, 2009) was used for statistical analysis of the associations between shape/SA/CT and cortical/regional SUVR.

In order to specify the most adequate model in each regression analysis, the following procedure was performed: First, the relevance of each of the following potential covariates was assessed by using the covariate and cortical or regional SUVR as regressors: age (in years), sex, education (in years), total intracranial volume, APOE genotype. Second, a regression model was specified retaining only the significant covariates as regressors. **Models testing associations between volumes and SUVR did not include total intracranial volume as a covariate because these volumes were normalized by total intracranial volume. In the present sample, education and APOE genotype did not significantly predict hippocampal volume, thalamic volume, striatal volume, shape or CT.**

Associations between volumes and SUVR

All volumes were adjusted for total intracranial volume using a method described previously (Buckner *et al.*, 2004). In order to investigate the associations between SUVR and hippocampal total and subfield volumes as well as thalamic and striatal volumes, regression models were specified with volume as regressand and cortical or regional SUVR as regressor. **First, these 32 models were specified including age, sex, education and APOE genotype as covariates. In these 32 models, education was never a significant covariate, APOE genotype was significant three times, age 24 times and sex 28 times. Therefore, regression models using age and sex as covariates were specified to investigate the associations between SUVR and volumes.** The resulting p-values were Benjamini-Hochberg FDR-corrected for multiple comparisons with number of comparisons m set to 12, taking into consideration the high dependency of hippocampal subfield volumes from each other and total hippocampal volume.

Associations between shapes or SA and SUVR

In order to investigate the association between shapes and cortical or regional SUVR, a regression model was specified at each vertex with displacement as regressand and cortical or regional SUVR as regressor. **First, these 12 models were specified including age, sex, education, total intracranial volume and APOE genotype as covariates. In these 12 models, age, education and APOE genotype were never significant covariates, total intracranial volume was significant 8 times and sex 12 times. Therefore, regression models using sex and total intracranial volume as covariates were specified to investigate the associations between SUVR and shapes.** In each of these cases, the resulting test statistics were FDR-corrected for multiple comparisons (Benjamini-Hochberg). FDR-

corrected values of $p < 0.05$ were considered significant.

In order to investigate the association between SA and cortical or regional SUVR, a regression model was specified at each vertex with SA as regressand and cortical or regional SUVR as regressor. **First, these 12 models were specified including age, sex, education, total intracranial volume and APOE genotype as covariates. In these 12 models, APOE genotype was never a significant covariate, education was significant once, sex was significant 5 times, age 8 times and total intracranial volume 12 times. Therefore, regression models using sex, age and total intracranial volume as covariates were specified to investigate the associations between SUVR and SA.** In each of these cases, the resulting test statistics were FDR-corrected for multiple comparisons (Benjamini-Hochberg). FDR-corrected values of $p < 0.05$ were considered significant.

Associations between CT and cortical SUVR

In order to investigate the association between CT of each hemisphere and cortical SUVR, a regression model was specified at each vertex with CT as regressand, cortical SUVR as regressor. First, these two models were specified including age, sex, education, total intracranial volume and APOE genotype as covariates. In both models, age and total intracranial volume were significant covariates. Therefore, regression models using age and total intracranial volume as covariates were specified to investigate the associations between cortical SUVR and CT. Again, the resulting test statistics were FDR-corrected for multiple comparisons (Benjamini-Hochberg). FDR-corrected values of $p < 0.05$ were considered significant. To determine the cortical regions wherein significant associations occurred, two separate atlases were used (Amunts *et al.*, 2005; Mai *et al.*, 2015).

Associations between cognitive performance and SUVR or volume

In order to confirm that cortical/regional SUVR and volume were not associated with cognitive performance in our sample of cognitively normal elderly subjects, regression models were specified for nine measures pertaining to memory and executive function (Table 2). For memory assessment, the German-language verbal learning and memory test "Verbaler Lern- und Merkfähigkeitstest" (VLMT) was used, providing learning, recall and recognition measures of verbal memory (Helmstaedter *et al.*, 2001; Volz-Sidiropoulou *et al.*, 2010). For assessment of executive function, the following neuropsychological measures were obtained: Digit span forward and backward from the Wechsler Memory Scale - Revised (Härting *et al.*, 2000), verbal (semantic) fluency and letter (phonemic) fluency from the CERAD-plus test battery (Thalmann *et al.*, 1997), the five point test (5PT) (Regard *et al.*, 1982; Kelemen & Fenton, 2010) and a measure from the trail making test (TMT) (Reitan, 1958) calculated by dividing the result of its B version by the result of its A version, which represents executive function.

Results

Associations between volumes and SUVR

Descriptive data for volumes and SUVR are shown in Table 1. Volumes of bilateral hippocampus and hippocampal subfields CA4/DG, CA2/CA3 and SRLM, left hippocampal subiculum and CA1 subfields as well as right thalamus were associated with cortical SUVR but not with regional SUVR (see Table 3).

Associations between shapes or SA and SUVR

Significant associations were found between left thalamic shape outward deformations and cortical SUVR in the region of its anterior nuclei (Figure 1A), as well as between left thalamic SA and regional SUVR in the area of its pulvinar (Figure 1B). Additionally, significant associations were found between left anterior hippocampal shape and regional SUVR, predominantly in its CA1 and subiculum regions, with dorsal outward and ventral inward deformations, respectively (Figure 1C).

Associations between CT and cortical SUVR

Significant negative associations between CT and SUVR were found for the left and right hemisphere. The areas of these associations corresponded highly between the hemispheres and occurred within the entorhinal cortex (EC) region (Figure 2).

Associations between cognitive performance and SUVR or volumes

Descriptive data for measures of cognitive performance are shown in Table 2. No associations between cognitive performance and SUVR (Table 4) or volumes (Table 5) were significant after Bonferroni-Holm correction for multiple comparisons.

Discussion

The goal of this study was to investigate structural brain changes in cognitively healthy elderly subjects with various degrees of cerebral amyloid-deposition. We showed that bilateral hippocampal volumes were not significantly associated with regional SUVR in

healthy subjects, extending findings from a study of patients with mild AD (Chang *et al.*, 2015). In contrast to our findings previous studies showed that hippocampal volumes were related to cortical PiB uptake in healthy elderly subjects (Hsu *et al.*, 2015; Mormino *et al.*, 2009), and a recent study using PiB PET and CSF tau and ptau to classify participants into stages of preclinical AD found smaller hippocampal volumes in later preclinical stages (Gordon *et al.*, 2016). Additionally, hippocampal atrophy in CA1 and the subiculum has been shown to predict progression to amnestic MCI in cognitively normal elderly individuals (Apostolova *et al.*, 2010). **Here, our findings would be consistent with the assumption that Aβ deposition precedes hippocampal atrophy (Jack *et al.*, 2013; Mormino *et al.*, 2009). With respect to the staging model of preclinical Alzheimer's disease (Sperling *et al.*, 2011) it could be that our population represents a very early stage with predominantly amyloid deposition without concomitant hippocampal atrophy.** Left hippocampal shape was not significantly associated with cortical, but with regional SUVR. These findings suggest that early hippocampal shape changes may reflect a localized reaction to amyloid deposition. Hippocampal shape has been shown to be associated with Aβ measured in CSF in healthy elderly individuals in a previous study (Carmichael *et al.*, 2012). This study derived shape measures from independent component analysis, where components defined a subregion of the three-dimensional hippocampus representation. In contrast, vertex-wise displacement values were used in the present study. Whereas CSF Aβ allows a global estimation of cerebral amyloid-deposition, by using amyloid-PET we were able to separately analyze cortical and regional SUVR in the present study. Hence, the present results are more informative with regard to the localization of significant associations between hippocampal shape and SUVR and they extended the previous findings by showing that hippocampal, but not cortical Aβ load was associated with hippocampal shape.

The localization of these associations to left anterior CA 1 corroborates previous findings in MCI patients (de Flores *et al.*, 2015) and is in line with a previous study on progression of non-demented elderly individuals to dementia due to AD (Csernansky *et al.*, 2005). This finding should be interpreted in the context of our results revealing entorhinal cortical thickness associations with cortical SUVR. The EC is affected early by tau pathology in AD (Braak & Braak, 1991a) and projects to the hippocampus via the perforant pathway, which is not only the primary input to the hippocampal formation, but also originates from cells that show neurofibrillary tangles in AD (Hyman *et al.*, 1986). Adding amyloid deposits to the perforant pathway terminal zone of neurons containing pathological tau has recently been shown to increase the extent of dystrophic axons and strongly alter the connectivity of these neurons in a transgenic mouse model (Pooler *et al.*, 2013). Thus, shape changes associated with amyloid-deposition may represent axonal damage due to amyloid toxicity in entorhinal neurons containing pathological tau. **Hippocampal SUVR has been shown to correlate with fluid attenuated inversion recovery intensities, indicating tissue edema, in cognitively normal elderly subjects (Schreiner *et al.*, 2014), supporting the view that a degenerative process underlies the association between hippocampal SUVR and shape found in the present study.**

Furthermore our analyses revealed significant associations between shape and cortical SUVR in the region of the anterior dorsal nuclei of the left thalamus. The anterior thalamic nuclei contain numerous neurofibrillary tangles in AD (Braak & Braak, 1991a) and are implicated in memory (Jankowski *et al.*, 2013). They have been shown to receive inputs from the subiculum in rat and monkey (Wright *et al.*, 2010; Aggleton *et al.*, 1986), a hippocampus region that has been shown to be affected early by histopathological events in AD in mice (Trujillo-Estrada *et al.*, 2014). In light of these findings, our results indicate that localized variations in left thalamic shape may reflect early changes in memory circuits preceding cognitive symptoms. The fact that left but not right thalamic shape was associated with

cortical SUVR is consistent with findings of asymmetrical brain changes in AD with left hemispheric predominance (Thompson *et al.*, 2003).

EC thickness was bilaterally associated with cortical SUVR consistent with an early involvement of the EC in the AD continuum. The EC is a region affected early by NFT pathology in AD (Braak & Braak, 1991b), and localized EC atrophy may accelerate up to 10 years before clinical symptom onset (Younes *et al.*, 2014). Because of the low number of individuals with high cortical SUVR, it may be argued that these outliers cause an overestimation of the true associations with CT. However, their localization is in striking correspondence with a previously reported AD cortical thinning signature in asymptomatic individuals (Dickerson *et al.*, 2009; Dickerson *et al.*, 2011).

We found no association between SUVR or volumes and a number of cognitive performance measures, which is consistent with the notion that the earliest pathological changes in AD may occur 10 to 20 years before symptom onset (Laske, 2014) and in line with a recent publication reporting no significant difference between amyloid positive and amyloid negative cognitively normal elderly individuals in verbal, visual and semantic memory, executive function and processing speed (Besson *et al.*, 2015).

One limitation of our study is the resolution of PET images, which prohibits more localized quantification of tracer uptake such as calculation of a separate SUVR for each hippocampal subregion. **Another limitation might be that we decided within this healthy group to not apply partial volume correction which could affect the accuracy of quantitative PET analysis (Rullmann *et al.*, 2016). Considering that we found no effect of volume on regional SUVR , we assume that there is no bias introduced by not applying a partial volume correction. Furthermore the regions of interest analyses were focused on individually segmented and grey matter delined regions reducing the general effect of atrophy on regional averages.**

Additionally, future studies should incorporate longitudinal data from cognitively normal elderly subjects progressing to MCI and cognitively stable elderly subjects in order to obtain quantitative estimates of the predictive value of local deformations of medial temporal lobe structures with regard to cognitive decline. Our CT results suggest that in addition to the hippocampus, the EC should be characterized in terms of shape using our methodology in order to compare the predictive value of changes in EC thickness with that of changes in EC shape. In conclusion, the results of the present study suggest that structural brain changes occur in association with amyloid deposition in presymptomatic AD and that these changes are detectable by measures of hippocampal shape and entorhinal cortical thickness. This positions these measurements as potential biomarkers of presymptomatic AD.

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Competing interests

The authors have no conflicts of interest.

Abbreviations

5PT = five point test

AD = Alzheimer's disease

CA = cornu ammonis

CERAD = Consortium to Establish a Registry for Alzheimer's Disease

CT = cortical thickness

DG = dentate gyrus

EC = entorhinal cortex

FDR = false discovery rate

ICV = intracranial volume

MCI = mild cognitive impairment

MRI = magnetic resonance imaging

NFT = neurofibrillary tangles

PET = positron emission tomography

PiB = Pittsburgh Compound B

SA = surface area

SRLM = strata radiata / lacunosum-moleculare

SUVR = standardized uptake value ratio

TMT = trail making test

VLMT = Verbaler Lern- und Merkfähigkeitstest

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Figure 1

Segmentation of the thalamus, the striatum and the five hippocampal subfields. Left-hemispheric structures are depicted.

Figure 2

L = left, R = right, A = anterior, P = posterior, S = superior, I = inferior.

A.: Colored areas show significant associations between thalamic shape and cortical SUVR using a FDR-corrected p value of 0.05. Scatterplots on the right-hand side illustrate disperson of values at peak vertices (minimal and maximal t value). Dorsal view of bilateral thalamus shows associations between outward deformations and cortical SUVR in the area of the left anterior dorsal nuclei.

B.: Colored areas show significant associations between thalamic SA and regional SUVR using a FDR-corrected p value of 0.05. This posterior view of bilateral thalamus shows negative associations between SA and regional SUVR in the area of the left mediodorsal nucleus. Scatterplot on the right-hand side illustrates disperson of values at the peak vertex (minimal t value).

C.: Colored areas show significant associations between hippocampal shape and regional SUVR using a FDR-corrected p value of 0.05. Scatterplots on the right-hand side illustrate disperson of values at peak vertices (minimal and maximal t value). Upper row: Dorsal view of bilateral hippocampus shows associations between outward deformations and regional SUVR in the area of the left anterior hippocampus. Lower row: Ventral view of bilateral hippocampus shows associations between inward deformations and regional SUVR.

Figure 3

Upper row: Colored areas show significant associations between CT and cortical SUVR using a FDR-corrected p value of 0.05. This medial view of both hemispheres shows negative associations between CT and cortical SUVR in the area of bilateral EC. Lower row: Scatterplots illustrate disperson of values at peak vertices (minimal t values).

Table 1. **Descriptive data for all control, volume and SUVR variables**

Variable	M	SD
Age (years)	68.087	6.029
Education (years)	15.101	2.739
ICV (cubic centimeters)	1326.871	205.983
Volume of left hippocampus*	17.446	2.467
Volume of right hippocampus*	17.242	2.405
Volume of left CA1*	5.471	0.733
Volume of right CA1*	5.560	0.749
Volume of left subiculum*	2.459	0.371
Volume of right subiculum*	2.684	0.407
Volume of left CA4/DG*	4.269	0.683
Volume of right CA4/DG*	4.254	0.643
Volume of left CA2/CA3*	1.162	0.211
Volume of right CA2/CA3*	1.074	0.236
Volume of left SRLM*	4.086	0.649
Volume of right SRLM*	3.669	0.603
Cortical SUVR	1.245	0.275
SUVR of left hippocampus	1.238	0.106
SUVR of right hippocampus	1.235	0.098
SUVR of left thalamus	1.425	0.193
SUVR of right thalamus	1.404	0.176
SUVR of left striatum	1.342	0.256
SUVR of right striatum	1.343	0.252

M = mean, SD = standard deviation, ICV = intracranial volume, CA = cornu ammonis, DG = dentate gyrus, SRLM = strata radiata/lacunosum-moleculare, SUVR = standardized uptake value ratio

* adjusted for ICV and multiplied by 10^4

Table 2. **Neuropsychological measures, descriptive data and covariates used in regression analyses**

Neuropsychological measure	Cognitive domain	Significant covariates		M	SD
		SUVR	Volume		
VLMT	Verbal memory - acquisition[a]	Sex	Sex, ICV (left thalamus: sex)	55.014	8.13
	Verbal memory - recall[b]	**Genotype**	**Genotype**	**11.333**	**2.465**
	Verbal memory - recognition[c]	Age, Sex	Age, Sex (left striatum: sex)	12.681	2.648
Digit span forward	Working memory	None	None	7.072	1.621
Digit span backward	Executive function	Education	Education	6.565	1.736
Verbal (semantic) fluency (animals)	Executive function	Genotype	Genotype (left thalamus: none)	24.406	6.013
Letter (phonemic) fluency (S words)	Executive function	None	None	30.522	10.997
5PT	Executive function	None	None	28.116	7.565
TMT B/A	Executive function	None	None	2.537	0.96

VLMT = Verbaler Lern- und Merkfähigkeitstest, 5PT = 5 point test, TMT = trail making test (versions A and B), ICV = intracranial volume

[a] This measure is the sum of the immediate recall from 5 consecutive runs of learning 15 words.

[b] This measure is the delayed recall score.

[c] This measure is the difference between the number of correctly recognized and the number of falsely identified words out of a list of previously presented and new words

Table 3. **Associations between SUVR and volumes**

Volume of interest		cortical SUVR				regional SUVR			
		t value	p value	Rank	(i/m)Q	t value	p value	Rank	(i/m)Q
Thalamus	left	-1.138	0.259	12	0.050	0.046	0.963	29	0.121
	right	-1.371	0.175	10	0.042	-0.915	0.363	13	0.054
Striatum	left	-0.037	0.971	31	0.129	0.044	0.965	30	0.125
	right	0.351	0.727	21	0.088	0.224	0.824	26	0.108
Hippocampus	left	-1.827	0.072	4	0.017	0.239	0.812	25	0.104
	right	-1.265	0.210	11	0.046	0.690	0.493	18	0.075
CA1	left	-1.699	0.094	5	0.021	0.291	0.772	22	0.092
	right	-0.849	0.399	14	0.058	0.846	0.401	15	0.063
CA2/3	left	-2.020	0.047	2	0.008	0.265	0.792	23	0.096
	right	-2.298	0.025	1	0.004	0.721	0.473	16	0.067
CA4/DG	left	-1.401	0.166	8	0.033	0.562	0.576	20	0.083
	right	-1.388	0.170	9	0.038	0.223	0.824	27	0.113
Subiculum	left	-1.468	0.147	6	0.025	-0.167	0.868	28	0.117
	right	-0.605	0.548	19	0.079	0.252	0.802	24	0.100
Stratum	left	-1.864	0.067	3	0.013	-0.016	0.987	32	0.133
	right	-1.456	0.150	7	0.029	0.721	0.473	17	0.071

i = Rank, m = 12 (number of comparisons), Q = 0.05 (significance threshold)

SUVR = subjective uptake value ratio, CA = cornu ammonis, DG = dentate gyrus

Regression models using age and sex as covariates were specified to investigate the associations between SUVR and volumes.

Table 4. **Associations between SUVR and cognitive performance**

Neuropsychological measure		Tracer uptake region						
		Neocortex	Thalamus		Striatum		Hippocampus	
			left	right	left	right	left	right
Digit span forward	t value	0.314	-0.235	-0.566	0.106	-0.014	-1.563	-1.285
	p value	0.754	0.815	0.574	0.916	0.988	0.123	0.203
	Rank	49	56	36	59	63	7	12
	(i/m)Q	0.039	0.044	0.029	0.047	0.050	0.006	0.010
Digit span backward	t value	-1.567	-0.680	-0.468	-1.398	-1.481	-0.527	-1.116
	p value	0.122	0.499	0.642	0.167	0.143	0.600	0.269
	Rank	6	33	42	10	8	40	15
	(i/m)Q	0.005	0.026	0.033	0.008	0.006	0.032	0.012
Verbal fluency - categorical	t value	0.848	0.579	0.916	1.096	0.773	0.808	0.356
	p value	0.400	0.565	0.363	0.277	0.442	0.422	0.723
	Rank	24	35	21	16	27	26	46
	(i/m)Q	0.019	0.028	0.017	0.013	0.021	0.021	0.037
Verbal fluency - phonemic	t value	-0.265	-0.760	-1.254	-0.281	-0.711	1.087	0.698
	p value	0.792	0.450	0.214	0.780	0.480	0.281	0.488
	Rank	54	29	13	52	31	17	32
	(i/m)Q	0.043	0.023	0.010	0.041	0.025	0.013	0.025
Verbal memory - acquisition (VLMT)	t value	0.384	0.253	1.452	-0.046	0.553	0.431	0.552
	p value	0.702	0.801	0.151	0.963	0.582	0.668	0.583
	Rank	44	55	9	62	37	43	38
	(i/m)Q	0.035	0.044	0.007	0.049	0.029	0.034	0.030
Verbal memory - recall (VLMT)	t value	0.094	-0.090	0.190	-0.306	0.285	1.070	1.712
	p value	0.926	0.929	0.850	0.761	0.776	0.289	0.092
	Rank	60	61	57	50	51	19	4
	(i/m)Q	0.048	0.048	0.045	0.040	0.040	0.015	0.003

Verbal memory - recognition (VLMT)	t value	1.076	-0.381	-0.120	0.504	0.856	0.927	1.137
	p value	0.286	0.705	0.905	0.616	0.395	0.358	0.260
	Rank	18	45	58	41	23	20	14
	(i/m)Q	0.014	0.036	0.046	0.033	0.018	0.016	0.011
5PT	t value	1.596	-0.329	-0.266	0.814	0.673	-0.749	-0.904
	p value	0.115	0.743	0.791	0.418	0.503	0.456	0.369
	Rank	5	47	53	25	34	30	22
	(i/m)Q	0.004	0.037	0.042	0.020	0.027	0.024	0.017
TMT B/A	t value	1.866	0.328	2.027	1.364	2.337	0.546	0.773
	p value	0.066	0.744	0.047	0.177	0.022	0.587	0.442
	Rank	3	48	2	11	1	39	28
	(i/m)Q	0.002	0.038	0.002	0.009	0.001	0.031	0.022

i = Rank, m = 63 (number of comparisons), Q = 0.05 (significance threshold)

Table 5. **Associations between volumes and cognitive performance**

Neuropsychological measure		Region					
		Thalamus		Striatum		Hippocampus	
		left	right	left	right	left	right
Digit span forward	t value	-1.807	-1.718	-0.851	-0.969	-1.664	-1.484
	p value	0.075	0.091	0.398	0.336	0.101	0.143
	Rank	9	11	27	26	13	19
	(i/m)Q	0.008	0.010	0.025	0.024	0.012	0.018
Digit span backward	t value	-1.786	-1.603	-2.016	-1.426	-2.082	-1.126
	p value	0.079	0.114	0.048	0.159	0.041	0.264
	Rank	10	15	5	20	3	23
	(i/m)Q	0.009	0.014	0.005	0.019	0.003	0.021
Verbal fluency - categorical	t value	2.165	1.689	0.757	0.519	0.043	0.774
	p value	0.034	0.096	0.452	0.605	0.966	0.442
	Rank	2	12	31	35	51	29
	(i/m)Q	0.002	0.011	0.029	0.032	0.047	0.027
Verbal fluency - phonemic	t value	0.227	0.177	-0.131	-0.157	-0.237	-0.761
	p value	0.821	0.860	0.896	0.876	0.813	0.449
	Rank	42	44	47	45	41	30
	(i/m)Q	0.039	0.041	0.044	0.042	0.038	0.028
Verbal memory - acquisition (VLMT)	t value	0.512	1.553	2.024	1.661	1.976	2.243
	p value	0.610	0.125	0.047	0.102	0.052	0.028
	Rank	36	16	4	14	6	1
	(i/m)Q	0.033	0.015	0.004	0.013	0.006	0.001
Verbal memory - recall (VLMT)	t value	-0.249	-0.125	0.017	0.034	0.363	1.068
	p value	0.804	0.901	0.986	0.973	0.718	0.290

	Rank	40	48	53	52	39	24
	(i/m)Q	0.037	0.044	0.049	0.048	0.036	0.022
Verbal memory - recognition (VLMT)	t value	0.384	0.225	1.387	0.527	0.847	0.981
	p value	0.702	0.823	0.170	0.600	0.400	0.330
	Rank	38	43	21	34	28	25
	(i/m)Q	0.035	0.040	0.019	0.031	0.026	0.023
5PT	t value	-1.857	-1.899	-0.399	-0.709	-1.526	-1.498
	p value	0.068	0.062	0.691	0.481	0.132	0.139
	Rank	8	7	37	32	17	18
	(i/m)Q	0.007	0.006	0.034	0.030	0.016	0.017
TMT B/A	t value	0.047	0.011	0.054	-0.139	0.681	1.215
	p value	0.963	0.991	0.957	0.890	0.498	0.229
	Rank	50	54	49	46	33	22
	(i/m)Q	0.046	0.050	0.045	0.043	0.031	0.020

i = Rank, m = 54 (number of comparisons), Q = 0.05 (significance threshold)